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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/782,953 | 02/13/2001 | R. Sanders Williams | UTSD:674US/SLH | 2337 |

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| EXAMINER | |
|---|---|
| LIU, SAMUEL W | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | 18 |

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/782,953 | WILLIAMS ET AL. | |
| | Examiner | Art Unit | |
| | Samuel W Liu | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication (35 U.S.C. § 133).
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *16 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-101* is/are pending in the application.

4a) Of the above claim(s) *1-58,63-69 and 71-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *59-62 and 70* is/are rejected.

7)☒ Claim(s) *70* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

Applicants' amendment filed 16 June 2003 (Paper No.16) as to amendment of claims 59 and 61, and applicants' request filed 16 June 2003 (Paper No. 15) for exertion of time of one month have been entered. Claims 59-62 and 70 are pending to which the following is or remains applicable. Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

### *Objection to Declaration under 37 C.F.R. 1.131*

Declaration under 37 C.F.R. 1.131 filed 16 June 2003 has not been entered because it is unsigned.

### *Claim/specification Objections*

The disclosure is objected to because of the following informalities:

In claim 70, the article "a" should be added before the recitation "cardiac disease".

In page 84, line 29, "MgCL2" should be changed to "$MgCl_2$".

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 59-62 and 70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 59 recites "modulation"; the recitation is not clear as to whether or not the modulation refers to up- or down-regulation. The dependent claims are also rejected.

Claim 60 recites "muscle cell is located in a mammal"; the recitation is not apparent as to whether or not the muscle cell does not originate from the said mammal but is transplanted into the mammal instead.

Claim 70 is indefinite because the recitation "a pharmaceutical agent" is not clear as to whether or not the pharmaceutical agent comprises the modulator recited in claim 59.

*Response to the rejection under 35 USC 112, the second paragraph*

The response filed 16 June 2003 argues that the term "modulation" is the very point of the claim and not infinite (see page 5). The applicants' argument is found unpersuasive because a method of up-regulation and a method of down-regulation are mutually exclusive in that they reach opposing endpoints, and in that they employ structurally distinct *agonists* or *antagonists* to accomplish these mutually exclusive endpoints.

***Claim Rejections - 35 USC §102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 59 and 61 are again rejected under 35 U.S.C. 102 (a) as being anticipated by Fuentes, J. *et al.* (*Human Mol. Genet.* (July 1, 2000) 9, 1681-1690).

Fuentes *et al.* teaches that DSCR1 encoded protein (*i.e.*, MCP1), and that the DSCR1 transcript is expressed in human heart and skeletal muscles (see "Introduction" section) and the expression is stimulated by calcium and calcium biding protein, *i.e.*, calmodulin (see page 1687, the third paragraph and Figure 7 data), as applied to claim 59 and 61.

Claims 59-62 and 70 are again rejected under 35 U.S.C. 102 (a) as being anticipated by Rothermel, B. *et al.* (*J. Biol. Chem.*, (March 24, 2000) 275, 8719-8725).

Rothermel *et al.* teach a process of regulating mammalian myoblast growth by MCIP1 protein which is up-regulated during muscle differentiation, and *co-expression* of the polypeptide, *i.e.*, calcineurin, in myocytes promotes expression of MCIP1 protein in cytoplasm (see Figure 6A, and the right column, page 8723), as applied to application claims 59, 61 and 62.

The current disclosure is also directed to a therapeutic method for treating muscle cells in a mammal that has a muscular cell associated disorder/disease by modulating MCIP1 expression. Accordingly, Rothermel *et al.* teach that the gene encoding MCIP1 is located on human chromosome 21 is a therapeutic target for cardiac-myocyte associated disorders (se the last paragraph, page 8725). The Rothermel teaching is applied to claims 60. Further, Rothermel et al. teach administering a polypetide, i.e., cyclosporin for preventing a cardiac disease state, e.g., cardiac hypertrophy, in a subject (see page 8725, the left column, the second to the last

paragraph). Thus, the Rothermel et al. teaching anticipates claims 70 of the instant application as well.

Therefore, the Rothermel *et al.* reference anticipates claims 59-62 and 70 of the current application.

*Response to the rejections under 35 USC 102(a)*

Applicants argue against the claim rejections over Fuentes et al. and Rothermel et al. based on the applicants' Declaration under 37 C.F.R. 1.131. The rejections are maintained in light of the defective Declaration under 37 C.F.R. 1.131 filed 16 June 2003 because it is unsigned (see page 3 of the Declaration wherein inventors Beverly Rothermel and R. Sanders Williams do not sign).

*The following is the new ground of rejection*

Claims 59-60 and 70 are rejected under 35 U.S.C. 102 (b) as being anticipated by Chin, E. R. et al. (*Gene Dev.* (1998) 12, 2499-2509) as is evidenced by Rothermel, B. *et al.* (*J. Biol. Chem.* (2000) 275, 8719-8725).

Chin et al. teach a process of modulating skeletal and cardiac muscle cell growth comprising providing a peptide modulator for calcineurin, i.e., cyclosporin, and administering the cyclosporin polypeptide to the subject (see abstract and pages 2502-2503, the section "*administration of the calcineurin antagonist cyclosporin A to intact animal promotes slow-to-fast fiber transformation*"). The Chin et al. teaching is applicable to the limitation of claims 59-60 of the current application. Note that the current invention is directed to a method of

modulating muscle cell growth by administering to a subject a polypeptide modulator but NOT to a method of modulating MCIP1 expression, and that the modulator regulation of MCIP1 is regarded as a mechanistic step, which is an inherent property of calcineurin action as is evidenced by Rothermel's reference where shows that calcineurin modulates MCIP1 through a direct interaction of the calcineurin catalytic domain with MCIP1 protein (see abstract) and that MCIP1 is a target for modulation by calcineurin antagonist, i.e., cyclosporin (*ibid*, the second to the last paragraph). Thus, the Chin et al. teaching anticipates claims 59-60 of the current application.

Also, Chin et al. teach that the modulation stated above has medical application, e.g., treating for cardiac hypertrophy that is a cardiac disease (see page 2506), which anticipates claim 70 of the current application.

Claims 59-60 and 70 are rejected under 35 U.S.C. 102 (b) as being anticipated by Sussman M. A. et al. (*Science* (1998) 281, 1690-1693) as is evidenced by Yang, J. et al. (Cir. Res. (2000) 87, e61-e68).

Sussman et al. teach a process of modulating cardiac muscle cell growth, e.g., preventing cardiac hypertrophy in mice comprising providing a peptide modulator for calcineurin, i.e., cyclosporin, and administering the cyclosporin to the patient (see abstract, Figures 1-2, and pages 1690-1691 and 1693), wherein calcineurin is an activator for induction of MCIP1 expression as is evidenced by Yang et al. The Sussman et al. teaching anticipates claims 59-60 of the current application. It is of note that the current invention is directed to a method of modulating muscle cell growth by administering to a subject a polypeptide modulator but NOT to a method of

modulating MCIP1 expression, and that up-regulation of MCIP1 expression is an inherent property of calcineurin.

Also, Sussman et al. teach that the cyclosporin therapy for cardiac disease, e.g., cardiac hypertrophy, (see page 1690 and the last paragraph of 1693), which anticipates claim 70 of the current application.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

Samuel W. Liu, Ph.D.

August 1, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER